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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,817	12/20/2004	Andrew Bailey	100727-1P US	9954

22466 7590 09/26/2005

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GLOBAL INTELLECTUAL PROPERTY
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EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 09/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/518,817	BAILEY ET AL.	
	Examiner	Art Unit	
	Venkataraman Balasubramanian	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9 and 10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/20.2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The preliminary amendment w, which included cancellation of claim 8 and amendment to claims 1-7, filed on 12/20/2004, is made of record. Claims 1-7, 9 and 10are pending.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-7, 9 and 10, drawn to compound of formula I wherein X is C-A, namely pyrimidine compound, composition and method of use, classified in class 544, subclasses 319, 298, class 514, subclass 269.

II. Claims 1, 3-7, 9 and 10, drawn to a compound of formula I wherein X is N, namely triazine compound, composition and method of use, classified in class 544 subclass 219, class 514, subclass 241.

The inventions are distinct, each from the other because of the following reasons:

As per MPEP § 803, there are two criteria for a proper requirement for restriction between patentably distinct inventions:

(A) The inventions must be independent or distinct as claimed and

(B) There must be a serious burden on the examiner if restriction is required.

Invention I and II are independent and distinct from each other because they are directed to structurally dissimilar compounds with distinct X choice that lack common core, namely pyrimidine core versus triazine .Consequently, the groups have different classifications and require separate prior art searches. They can be made and used independently. Art which may render obvious or anticipate one of the groups would not

necessarily do the same for the other group. For example prior art cited in the Information Disclosure Statement may not be applicable to all the above groups. Each can support a patent as the compounds of each group are capable of being utilized alone not in combination with other members listed in the Markush group.

In addition, it is necessary to classify and search all the controlling cores generically embraced in Group I and II along with various choices of heterocyclic ring embraced variable groups. Such a search of all controlling cores would serious search burden.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

During a telephone conversation with Shianzhong Shen on 9/12/2005 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-7, 9 and 10. Affirmation of this election must be made by applicant in replying to this Office action. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claims 1-7, 9 and 10 will be examined to the extent they embrace the elected subject matter.

Information Disclosure Statement

References cited in the Information Disclosure Statement, filed on 12/20/2004, are made of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7, 9 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Any claim not specifically rejected is rejected as it is dependent o n a rejected claim and shares the same indefiniteness.

1. Recitation of "and pharmaceutically acceptable salts or solvates thereof " in claims 1, and 7 as well as recitation of ""and pharmaceutically acceptable salts or thereof in claim 6 renders these claims and their dependent claims indefinite, as it is not clear whether these claims are compound claim or a composition claim containing the salts. Note Markush recitation should be in alternate and singular form. Replacement of "salts" with "salt" is suggested.

2. Recitation of " in the manufacture of a medicament for use in the inhibition of cathepsin S in mammal such as man" in claim 1 renders claim 1 and claims 2-6 indefinite as it is not clear whether thee claim is a method of use claim as recited in line 1 or a the claim related manufacturing of medicament. An appropriate correction is needed.

3. Claim 2 is an improper dependent claim as it recites X as CH, NHR^2, OR^2 while in claim 1 X is N or CA.

Claims 1-16 and 20-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making pharmaceutically acceptable salts does not reasonably provide enablement for making solvate or hydrate. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The following apply.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1. **The nature of the invention and the state of the prior art:**

The invention is drawn to compound of formula I, or a pharmaceutically acceptable salt solvate or hydrate thereof. Specification is not adequately enabled as to how to make hydrate of compounds of formula (I) Specification has no example of hydrate of the instant compounds. Specification on page 33 recites solvate or hydrate thereof but there is no enabling of such compounds.

The compound of formula I embrace 2, 4-substitutedamino–5-trifuloromethyl-pyrimidine compounds substituted with variable groups R^1, R^2, R^3 and R^4.

Even a cursory calculation of the number of compounds embraced in the instant formula (I) based on the generic definition of alkyl., aryl heteroaryl, heterocyclyl, substituted aryl, heteroaryl, arylalkyloxy, arylalkylthio etc would result in millions and millions of compounds. This is of course not the accurate number and the true number of compounds would far exceed this number of compounds. Thus the genus embraced in the claim 1 is too large and there is no teaching of any hydrate of this large genus.

Search in the pertinent art, including water as solvent resulted in a pertinent reference, which is indicative of unpredictability of hydrate formation in general. The state of the art is that is not predictable whether solvates or hydrates will form or what their composition will be. In the language of the physical chemist, a hydrate of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is the compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometery of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. Compared with polymorphs, there is an additional degree of freedom to hydrates, which means a different solvent or even the moisture of the air that might change the stabile region of the hydrate. In the instant case of hydrate a

similar reasoning therefore apply. Water is a solvent and hence it is held that a pertinent detail of West, which relates to solvates, is also applicable to hydrate

In addition, an additional search resulted in Vippagunta et al., Advanced Drug Delivery Reviews 48: 3-26, 2001, which clearly states that formation of hydrates in unpredictable. See entire document especially page 18, right column section 3.4. Note Vippagunta et al., states "Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for series of related compounds".

2. **The predictability or lack thereof in the art:**

Hence, the solvate and hydrate as applied to the above-mentioned compounds claimed by the applicant are not art-recognized compounds and hence there should be adequate enabling disclosure in the specification with working example(s).

3. **The amount of direction or guidance present:**

Examples illustrated in the experimental section are limited to making the compounds not related to solvates and hydrates. There is no example of a solvate or hydrate of instant compound. Thirty-one compounds were shown in the examples of the specification each of which has come in contact with water and other solvent but there is no showing that instant compounds formed solvates or hydrates. Hence it is clear that merely bring the compound with solvent or water does not result in solvate or hydrate and additional direction or guidance is needed to make them Specication has no such direction or guidance.

4. **The presence or absence of working examples:**

There is no working example of any solvate or hydrate formed. The claims are drawn to hydrate, yet the numerous examples presented all failed to produce a solvate or hydrate or even hydrate. These cannot be simply willed into existence. As was stated in Morton International Inc. v. Cardinal Chemical Co., 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there, is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ...' no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that hydrates of these compounds actually exists; if they did, they would have formed. Hence, there should be showing supporting that solvates and hydrates of these compounds exist and therefore can be made.

5. **The breadth of the claims & the quantity of experimentation needed:**

Specication has no support, as noted above, for compounds generically embraced in the claim 1 would lead to desired solvate and hydrate of the compound of formula I. As noted above, the genus embraces over million compounds and hence the breadth of the claim is broad. The quantity of experimentation needed would be an undue burden on skilled art in the chemical art since there is inadequate guidance given to the skilled artisan for the many reasons stated above. Even with the undue burden of experimentation, there is no guarantee that one would get the product of desired hydrate of compound of formula I embraced in the instant claims in view of the pertinent reference teachings.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to make Applicants' invention.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 and 10 are rejected under U.S.C. 112, first paragraph, because the specification while being enabling for treating rheumatoid arthritis, does not reasonably provide enablement for treating any or all disease or disorders mediated by cathepsin S and cysteine protease. The specification does not enable any physician skilled in the art of medicine, to use the invention commensurate in scope with these claims.

The instant method of use claims 1-4 and 10 are drawn as reach through claims based on the mode of action of instant compounds as cathepsin S and cysteine protease inhibitors. A reach through claim is a claim wherein a mode of action of a genus of compound is disclosed and then based on the mode of action treatment of any or all diseases mediated through the mode of action is claimed. In the instant case, based on the mode of action of instant compounds as cathepsin S and cysteine protease inhibitors treatment of any or all diseases and disorders is embraced in the

claim language. The scope of the claims includes as recited any or all diseases including inflammation and immune disorders such as asthma, rheumatoid arthritis, COPD, multiple sclerosis, Crohn's disease, Alzheimers and pain, such as nemopathic pain, which is not adequately enabled solely based on the activity of the compounds provided in the specification. The instant compounds are disclosed to have cathepsin S and cysteine protease inhibitory activity and it is recited that the instant compounds are therefore useful in treating any or all diseases stated above for which applicants provide no competent evidence. It appears that the applicants are asserting that the embraced compounds because of their mode action as cathepsin S and cysteine protease inhibitor that would be useful for all sorts of diseases including inflammation and autoimmune diseases. However, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host. Moreover many if not most of diseases such as multiple sclerosis, Alzheimer's disease etc,. are very difficult to treat and despite the fact that there are many compounds which act are known to act on "inflammation".

The scope of the claims involves thousands of compounds of claims 1 and 7 as well as the thousand of diseases embraced by the reach through claim language.

In addition, claim 10 is deemed as reach through claim wherein a mode of action is recited first and then all or any diseases that relate to the mode of action is claimed. In the instant case because of the mode of action as cathepsin S and cysteine protease inhibitor, the instant compounds are implied to be useful for treating any or all diseases .

No compound has ever been found to treat diseases of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "compound" is contrary to our present understanding of modern medicine. Thus, it is beyond the skill of physician today to get an agent to be effective against all diseases generally. Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Next, applicant's attention is drawn to the Revised Utility and Written Description Guidelines, at 66 FR 1092-1099, 2001 wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. See Hou et al. Arthritis & Rheumatism, 46(3): 663-674, 2002.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating disorders/diseases that require cathepsin S and cysteine protease inhibitory activity.

2) The state of the prior art: Recent publications expressed that the cathepsin S and cysteine protease inhibition effects are unpredictable and are still exploratory. See Hou et al., cited above.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for r treating any or all cancers or abnormal cell growth of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show treating any or all cancers or abnormal cell growth and the state of the art is that the effects of cathepsin S and cysteine protease inhibitors are unpredictable.

6) The breadth of the claims: The instant claims embrace any or all diseases including those yet to be related to cathepsin S and cysteine protease .

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of enzyme-inhibitor interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was 'filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 7 is rejected under 35 U.S.C. 102(b) as being anticipated by Niedermann et al. US 5,759,956.

See column 12, example 18 , wherein Niedermann et al teaches two compounds which are also claimed in the instant claim.

Claim 7 is rejected under 35 U.S.C. 102(b) as being anticipated by Tomota JP 06135942, CA 121: 179610, 1994 (CAPLUS Abstract also provided)

See compound shown in the CAPLUS Abstract.

Claim 7 is rejected under 35 U.S.C. 102(b) as being anticipated by Taube DE 870304.

See example 4, line 38 of page 2.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5 and 7-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Altman et al. WO 03/020278.

. Wood et al. teaches several variously substituted 2-cyano-pyrimidine compounds for treating rheumatoid arthritis, which include compounds, and the method of use of claimed in the instant claims. See page 1, formula I and note when R choice is OR4 or NR3R4 and R1 is CH_2NR5R6, compounds taught by Altman et al., includes instant compounds. See pages 1-16 for details of the invention and pages 17-52 for examples of various compounds made.

Although Altman et al., exemplifies large number of 2-cyanopyrimidine compounds, all of them are limited R =H, not OR4 or NR3R4. However, Altman et al. teaches the equivalency of those compounds exemplified with specific substituents with that generically recited for compound of Formula I in page 1.

Thus, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make 2-cyanopyrimidine compounds variously substituted with R, R1 and R2 including R = OR4 or NR3R4 as permitted by the reference and expect resulting compounds (instant compounds) to possess the uses taught by the art in view of the equivalency teaching outline above.

Conclusion

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Acting Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson, whose telephone number is (571) 272-0661.

The fax phone number for the organization where this application or proceeding is assigned (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

Venkataraman Balasubramanian

9/16/2005